Doc Code: AP.PRE.REQ

PTO/SB/33 (07-05)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
0380-P02709US0

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on October 19, 2006

Signature Tina M. Doyle

Typed or printed name Tina M. Doyle

Application Number	Filed
09/980,913	May 21, 2003

First Named Inventor: Ernest ARENAS

Art Unit	Examiner
1636	Laura McGillem

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 27,643.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Patrick J. Hagan
Signature

Patrick J. Hagan
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215-563-4100
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October 19, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

In view of the facts and argument presented below, applicants respectfully request review of the final rejection in the above-identified patent application in accordance with the Pre-Appeal Brief Conference Pilot Program established by PTO Official Gazette Notice dated 7/12/05.

I. STATEMENT OF FACTS

A. The Invention

The present invention is based on applicants' finding that dopaminergic neurons can be generated from multipotent neural stem cells or progenitor cells *in vitro* by a process involving expression of *Nurr*1 above basal levels in the neural stem cells or progenitor cells, and contacting such cells with one or more factors supplied by or derived from Type 1 astrocytes of the ventral mesencephalon.

The experimental results described in the present specification provide the first evidence that Type 1 astrocytes are involved in the determination of specific neuronal fates. These data indicate that astrocytes from distant brain regions can be utilized as a source of signals required for the induction of regionally appropriate neuronal phenotypes in multiple brain structures. See the present specification at page 34, lines 5-19; page 37, line 24 through page 38, line 27; page 41, lines 1-16; and page 42, lines 12-23.

B. The Claims

Claims 1-3 and 5-12 are currently pending. Claim 1, the only independent claim, reads as follows:

> 1. A method of inducing a dopaminergic neuronal fate in a neural stem cell or neural progenitor cell, the method comprising:
>
> expressing Nurr1 above basal levels within the cell, co-culturing the cell with a Type 1 astrocyte of the ventral mesencephalon, and thereby contacting the cell in vitro with one or more factors secreted from said Type 1 astrocyte of the ventral mesencephalon, whereby dopaminergic neurons are produced.

The claim term "neuronal stem cell or neural progenitor cell" is sometimes hereinafter expressed as "NSC/NPC".

C. Final Rejection and Request for Reconsideration

In the 4/19/06 Official Action, claims 1-3 and 5-12 stand finally rejected under 35 U.S.C. 103(a) as unpatentable over U.S. Patent 6,284,539 to Bowen et al. (Bowen), in view of Takeshima et al., Neuroscience, 60(3): 809-823 (1994) (Takeshima) for the reasons set forth in the 7/29/05 Official Action.

Bowen describes a method for generating dopaminergic cells by the introduction and endogenous expression in CNS stem cells of a gene coding for the nuclear receptor Nurr1 in order to direct such neuronal precursors to a dopaminergic cell fate which is verified by expression of tyrosine hydroxylase. See abstract and examples 1 and 2 of Bowen. In the background of the invention section, Bowen discloses that co-culturing dopaminergic neurons with striatal astrocytes or with conditioned media from striatal astrocytes has been shown to increase the survival of the neurons. See column 3, lines 11-25 of Bowen.

Bowen does not disclose that neuronal stem cells are co-cultured with Type 1 astrocytes of the ventral mesencephalon in order to induce the development of dopaminergic neurons. (See the 7/29/05 official Action, at 22, lines 1-3).

Takeshima describes the results of an investigation of astrocyte-dependent and astrocyte-independent phases of development and survival of neurons from the medial, ventral mesencephalon of the E14 rat in culture. The purpose of the investigation was to test the hypothesis that dopaminergic neurons were uniquely sensitive to factors produced by Type-1 astrocytes. The ultimate goal of this line of investigation, according to the authors, was to identify endogenous dopaminergic neurotrophic factors (NTF) that might be useful in treating Parkinson's disease. See page 810 of Takeshima. The investigation showed that when grown in a serum-supplemented medium with proliferating glia, the percentage of TH^+ neurons in the culture increased from an initial value of 20%, at 12 hours after plating, to 60% by the 21^{st} day in culture. The authors concluded that an astrocyte-derived NTF that is relatively specific for promoting the survival of the dopaminergic neuronal phenotype is believed to mediate the observed effect.

Based on the combined disclosures of Bowen and Takeshima, the examiner argued that:

> It would have been obvious to one of ordinary skill in the art to modify the teachings of Bowen et al. to include co-cultures of ventral mesencephalic astrocytes to support the growth and increase the survival of dopaminergic neurons with increased levels of Nurr1 because Bowen et al. discloses increased survival of dopaminergic neurons when in co-culture with astrocytes. Takeshima et al. teach using a culture of Type 1 astrocytes of the mesencephalon to support the growth of developing dopaminergic neurons derived from embryonic rat brains. The motivation to do so is the expected benefit as suggested by Bowen et al. and actually exemplified by Takeshima et al. of being able to produce a viable culture of dopaminergic neurons. There is a reasonable expectation of success in using ventral mesencephalic astrocytes to support the development of neurons since this has worked previously in the cited techniques.

A Request for Reconsideration was filed August 21, 2006, explaining that Bowen and Takeshima themselves provide no motivation for co-culturing a NSC/NPC with a Type 1 astrocyte of the ventral mesencephalon, as called for in claim 1. *Ex parte Leonard*, 187 USPQ 122 (Bd. Apps. 1974) and *Ex parte Levengood*, 28 USPQ 2d 1300 (BPAI 1993) were cited in support of applicants' position in this regard.

An Advisory Action was issued September 13, 2006 indicating that the Request for Reconsideration was considered, but did not put the application in condition for allowance.

II. REASON FOR REVIEW

Review of the final rejection is requested, as the examiner has failed to satisfy the criteria for establishing *prima facie* obviousness as set out in §706.02(j) of the Manual of Patent Examining Procedure (MPEP).

III. ARGUMENT

All of the claims require co-culturing the NSC/NPC with a Type-1 astrocyte of the ventral mesencephalon. This requirement is neither taught nor suggested by Bowen or Takeshima, as there is no description of co-culturing NSC/NPC with astrocytes in either Bowen or Takeshima. The material on which a method is carried out must be accorded weight in determining the non-obviousness of the method. *Ex parte Leonard, supra.* Thus, the third criteria of MPEP §706.02(j) is not satisfied.

There is nothing in the cited references themselves which would suggest to those skilled in the art that they should carry out the claimed method. The examiner concedes that Bowen is deficient in this regard. See the 7/29/05 Official Action at 22, lines 1-3. The motivation purportedly provided by Takeshima to do what applicants have done is illusory. As noted above, the examiner relies in particular on Takeshima's statement that, ". . . astrocytes derived from the ventral mesencephalon are the source of a putative factor that promotes the development of TH^+ neurons in culture in the short term". According to the examiner, this statement suggests co-culturing developing neurons with astrocytes. See 4/19/06 Official Action, page 4, 3rd paragraph. However, there is no mention of neuronal stem cells or neural progenitor cells in Takeshima. Indeed, the term "development of TH^+ neurons", as used in Takeshima, when properly considered in context, does not include NSC/NPC. Rather, the "development of TH^+ neurons" is properly interpreted as the maturation of the neurons, and not inducement of neuronal fate, as presently claimed. Takeshima refers, at page 816, under the heading "Discussion", to "three distinct phases of development" and at page 817 to "the distinct phases of development identified in this study". These phases of development are (i) a progressive neurite development phase; (ii) an adverse growth phase; and (iii) a surge of neuritic growth phase, as illustrated, in part, in Figure 5 of Takeshima. These are phases of development of cells already committed to a neuronal fate. Considering the limited context of "development" discussed in this reference, there is no factual basis provided in Takeshima for extrapolating the term "development of TH^+ neurons", so as to include neuronal stem cells or neural progenitor cells . Silence in a reference is not a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow. *In re Burt*, 148 USPQ 548 (CCPA 1966). Accordingly, the first of the criteria of MPEP §706.02(j) has not been fulfilled.

Given that there is no mention in Bowen or Takeshima of co-culturing NSC/NPC with astrocytes, and nothing in the references themselves to motivate those skilled in the art to perform such a method, it necessarily follows that those of ordinary skill in the art could not possibly have had a reasonable expectation of success. Therefore, the second of the criteria of §706.02(j) of the MPEP has not been met.

Notwithstanding the examiner's assertion to the contrary, applicants have not attacked the cited references individually. See applicants' August 21, 2006 Request for Reconsideration, pages 2-3. Takeshima does not remedy the deficiences of Bowen so as to lead those of ordinary skill in the art to the present invention.

The same decisional approach that was followed in *Ex parte Levengood*, *supra*, compels the conclusion that the present 35 USC §103(a) rejection of claims 1-3 and 5-12 based on the combined disclosures of Bowen and Takeshima is improper.

IV. CONCLUSION

For the reasons stated above, as well as those presented in applicants' responses to the 7/29/05 and 4/19/06 Official Actions, it is respectfully requested that the final rejection be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

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PJH:tmd